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EXAMINER	
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ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/766,528	SALZWEDEL ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,10,12,13 and 82-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *13* is/are allowed.

6)☒ Claim(s) *1-7,9,10,12 and 82-84* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 07 May 2008. Claims 8, 11, 14-81, 85 and 86 have been cancelled. Claims 1-7, 9, 10, 12, 13 and 82-84 are pending and currently examined.

Claim 1 is objected to because the amendment introduces a redundant phrase "said compound is a member of the betulin or betulinic acid group of compounds." Applicants may consider deleting the phrase "of compounds" after the word "group."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1-7, 9, 10, 12, 13 and 82-84 under 35 U.S.C. §112, second paragraph, as being indefinite is **withdrawn** in response to the Applicants' amendment changing the limitation "derivative" to "member" of the betulin or betulinic acid.

The rejection of claims 1-7, 9, 10, 12 and 82-84 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is maintained for the claim limitation "member of the betulin or betulinic acid." The claims

contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method of treating HIV-1 infection in a patient, comprising administering to a patient in need thereof a compound that inhibits p25 (CA-SP1) processing to p24 (CA), wherein the HIV-1 does not contain a mutation encoding a substitution of Ala to Val at a position corresponding to residue 364 or 366 of HIV-1 Gag (residue 1 of SP1) as compared to the sequence of the wild type strain NL4-3 or RF, and wherein said compound is a member of the betulin or betulinic acid, or a pharmaceutically acceptable salt of said member.

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." M.P.E.P. §2163.

M.P.E.P. § 2163 also states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus.

Although the M.P.E.P. does not define what constitutes a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims encompass a broad genus of betulin or betulinic acid. The claimed "member of the betulin or betulinic acid" reads on any compound with unlimited number and kinds of modification from the prototype structure of betulin or betulinic acid and is not adequately described in the specification.

The specification only provides description for one subspecies of HIV-1 Gag p25 processing inhibitor compound, 3-O-(3',3'-dimethylsuccinyl) betulinic acid or betulin (DSB). See specification page 11, paragraph [0044], and pages 50-60, Example 1-8. Although the specification presents examples of the derivatives of betulinic acid and betulin on page 30, paragraph [0084], there is no correlation between the Gag processing inhibition function and the compound structure beyond the DSB disclosed in the examples in the specification. Neither does the specification identify any partial structure of the claimed "member" that must be conserved to retain the function of inhibition of HIV-1 Gag p25 processing. Therefore, the specification lacks sufficient variety of species to reflect this variance in the genus of betulinic acid/betulin. Furthermore, the state of the art teaches that the targets of betulinic acid derivatives are varied, depending primarily on the side chain structures of the compounds. For example, betulinic acid derivatives with a side chain at C-3 can inhibit HIV-1 maturation

whereas betulinic acid derivatives with a side chain at C-28 can block HIV-1 entry (Huang *et al.*, 2004). Therefore, not every claimed member of the betulin/betulinic acid is correlated with the functional limitation of a compound that inhibits p25 (CA-SP1) processing to p24 (CA). Applicants have not conveyed with reasonable clarity to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed genus of betulin or betulinic acid members.

Response to Arguments

Applicant's arguments filed 07 May 2008 have been fully considered but they are not persuasive. Applicants argue the following points: (1) The term "member of the betulin or betulinic acid group of compounds" does not refer to new or unknown materials that ordinary skilled artisans would easily miscomprehend and the specification describes numerous examples of compounds that all have a betulin and betulinic acid backbone; and (2) The claim term itself readily conveys distinguishing information concerning the identity of the recited compounds so that persons of ordinary skill in the art could recognize the identities of members of the genus.

In response to Applicants' reference to the examples of betulin or betulinic acid set forth in the specification, the state of art clearly teaches that sharing a betulin and betulinic acid backbone does NOT correlate with the function of inhibiting p25 (CA-SP1) processing to p24 (CA), which requires a side chain at C-3, as evidenced by Huang *et al.* (2004).

In response to Applicants' contention that the claim term conveys distinguishing identity of the recited compounds, Examiner proffers evidence showing high level of variance and unpredictability in the HIV inhibition function in the genus of betulin and betulinic acid. The generic claim limitation "a member of betulin or betulinic acid" encompasses compounds with modifications such as a side chain at C-28 of the backbone, which clearly does not inhibit Gag p25 (CA-SP1) processing to p24 (CA) but inhibits fusion activity (Huang *et al.*, 2004). It has been known in the art that Anti-HIV-1 triterpenes are classified into five different classes depending on their action mechanism and their molecular targets: (1) entry inhibitors that block HIV adsorption or membrane fusion; (2) reverse transcriptase inhibitors; (3) protease inhibitors; (4) virus maturation inhibitors that do not inhibit HIV-1 protease; and (5) inhibitors with unknown mechanism of action (See Sami *et al.*, 2006). With such a variety of inhibition functions depending on the side chain structures, Applicants are clearly not in possession of the entire genus of the betulin or betulinic acid compounds because not every species of the genus meets the recited limitation of a compound that inhibits p25 (CA-SP1) processing to p24 (CA).

The same rationale applies to claim 12 because the claim limitation encompasses dimethylsuccinyl side chain at all carbon positions in the betulin and betulinic acid backbone, which would affect its target on the HIV viral structure.

The rejection of claim 13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification commensurate in scope is **withdrawn** in response to Applicants' amendment to the "mutation" limitation.

The rejection of claims 1-7, 9, 10, 12 and 82-84 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification commensurate in scope is maintained because the specification, while being enabling for treating non-DSB-resistant HIV-1 infection in a patient by inhibiting p25 (CA-SP1) processing to p24 (CA) with 3-O-(3',3'-dimethylsuccinyl)betulinic acid (DSB), does not reasonably provide enablement for treating HIV-1 and inhibiting p25 (CA-SP1) processing to p24 (CA) with any other member of betulin or betulinic acid.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors (MPEP §2164.01(a)). See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The instant claims are drawn to a method of treating HIV-1 infection in a patient, comprising administering to a patient in need thereof a compound that inhibits p25 (CA-SP1) processing to p24 (CA), wherein said compound is a member of betulin or betulinic acid, or a pharmaceutically acceptable salt of said member, and wherein the HIV-1 does not contain a mutation encoding a substitution of Ala to Val at a position corresponding to residue 364 or 366 of HIV-1 Gag (residue 1 of SP1) as compared to the sequence of either the wild type strain NL4-3 or the wild type strain RF.

The nature of the invention is an HIV-1 treatment with a small molecule chemical compound that inhibits HIV-1 Gag p25 (CA-SP1) processing to p24 (CA). The claims encompass a genus of unspecified compounds that are modified compounds or analogs of betulin or betulinic acid. The claims are of excessive breadth and encompass any given putative anti-HIV compound without providing any meaningful structural limitations concerning that member. The disclosure simply fails to support such breadth in the claim language.

The disclosure fails to provide sufficient working embodiments that support the entire scope of the claimed invention. While there are cell culture examples disclosed for the single species of DSB in isolated peripheral blood mononuclear cells (PBMC) (Example 1- 4), H9 cells (Example 5 and 7) and HeLa cells (Example 6), this compound does not represent all other betulin or betulinic acid members that fall within the scope of the invention.

The specification provides no guidance regarding practice of the entire scope of the claimed method. The amount of direction is limited to the DSB inhibitory effect on

HIV maturation in cell culture (spec. pages 53-54, Example 3, ¶159). There is no data that other members of betulin and betulinic acid compounds can inhibit HIV Gag p25 processing to p24. There is no structural guidance to the broad genus of unspecified members. In other words, the specification fails to disclose which chemical structure of DSB is critical for binding to Gag p25 (CA-SP1) and which partial structures are required for inhibiting the p25 processing to p24. Thus, the specification is no more than an undue invitation by the applicant to further experimentation with all members of the betulin and betulinic acid group to identify putative HIV maturation inhibitors other than DSB.

The state of the art shows a high level of unpredictability in the inhibition function depending on the side chain structures of the betulin and the betulinic acid compounds. For example, betulinic acid derivatives with a side chain at C-3 can inhibit HIV-1 maturation whereas betulinic acid derivatives with a side chain at C-28 can block HIV-1 entry (Huang *et al.*, 2004). Therefore, not every claimed member of the betulin/betulinic acid is capable of inhibiting HIV Gag p25 (CA-SP1) processing to p24 (CA), and hence, the cell culture characterization data for the inhibition mechanism of DSB cannot to extrapolated to every other member of the betulin and betulinic acid compounds. It has been known in the art that Anti-HIV-1 triterpenes are classified into five different classes depending on their action mechanism and their molecular targets: (1) entry inhibitors that block HIV adsorption or membrane fusion; (2) reverse transcriptase inhibitors; (3) protease inhibitors; (4) virus maturation inhibitors that do not inhibit HIV-1 protease; and (5) inhibitors with unknown mechanism of action (See Sami *et al.*, 2006). With such a

variety of inhibition functions depending on the side chain structures, the instant specification apparently does not support the full scope of the claimed method of inhibiting HIV Gag p25 (CA-SP1) processing to HIV Gag p24 (CA) with any member of the betulin and betulinic acid compounds.

Response to Arguments

Applicants' arguments filed 07 May 2008 have been fully considered but they are not persuasive. Applicants argue that: (1) the amendment filed on 18 July 2007 (page 18) presented evidence that two members of the recited compounds, PA-457 (DSB) and PA-040 (3-O-(3',3'-dimethylsuccinyl)-dihydrobetulinic acid or DSD), have entered into FDA-approved clinical trials for treatment of HIV-1 infection; (2) other members of the recited compounds were known compounds that had been found to have anti-HIV activity; (3) the FDA and other experts in the field provide a copious amount of guidance for carrying out this routine experimentation, including guidance for extrapolating the results of in vitro and animal experiments to humans.

First of all, the Examiner has fully considered the evidence submitted on 18 July 2007 regarding the clinical trial status of the DSB and DSD compounds, which is why the scope of enablement rejection in the previous Office Action mailed on 07 February 2008 stated: "the specification, while being enabling for treating non-DSB-resistant HIV-1 infection in a patient with DSB, does not reasonably provide enablement for treating HIV-1 with any other derivative of betulin or betulinic acid." The change in the limitation of "derivative" to "member" does not overcome this rejection because, as set forth

above, there is a high level of unpredictability and variance in the inhibition function depending on the side chain structures of the betulin and the betulinic acid compounds. In short, not every member of betulin and betulinic acid compounds is enabled for the claimed functional limitation of "a compound that inhibits p25 (CA-SP1) processing to p24 (CA)" in the instant claims. The FDA-approved DSB and DSD are not structural representatives of all the members of betulin or betulinic acid and therefore are not predictive of the Gag inhibition effectiveness of any other members of betulin or betulinic acid. Therefore, the evidence submitted by Applicants is not commensurate in scope with the claimed invention.

Secondly, the Examiner is fully aware of the fact that other members of the recited betulin and betulinic acid compounds were known compounds that had been found to have anti-HIV activity in HIV-infected cells as anti-HIV-1 triterpenes are classified into five different classes depending on their action mechanism and their molecular targets: (1) entry inhibitors that block HIV adsorption or membrane fusion; (2) reverse transcriptase inhibitors; (3) protease inhibitors; (4) virus maturation inhibitors that do not inhibit HIV-1 protease; and (5) inhibitors with unknown mechanism of action (See Sami *et al.*, 2006). However, the claimed invention is NOT anti-HIV betulin and betulinic acid compounds with anti-HIV activity. The claim language does not comply with Applicants' statement of the claimed invention here. Applicants seemed to have disregarded the claim limitation "a compound that inhibits p25 (CA-SP1) processing to p24 (CA)" as recited in claim 1, which is not fully enabled by the entire genus of betulin and betulinic acid members.

Lastly, the Examiner appreciates the FDA guidance provided by the Applicants. However, the FDA guidance does not help predict the maturation inhibition effectiveness for every member of the betulin and betulinic acid and does not address the problems with serum sequestration and plasma concentration, which directly affect the anti-HIV activity.

The rejection of claims 13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification commensurate in scope is **withdrawn** in light of the on-going clinical trials of the compounds, DSB and DSD, and the high degree of structural similarity among the recited compounds, *i.e.* the side chain structure at C-3, and further in response to the claim amendment narrowing the limitation to HIV-1 strains that do not contain DSB-resistance mutations A364V and A366V.

Allowable Subject Matter

The following is a statement of reasons for the indication of allowable subject matter: Claim 13 is free of prior art of the record. The closest prior art, US PAT. NO. 5,679,828 to Lee *et al.*, which teaches administering to an HIV-infected patient DSB and DSD (col. 6 and col. 7, lines 16-26), does not teach or fairly suggest treating the infection of the HIV that does not contain a mutation encoding a substitution of Ala to Val at a position corresponding to residue 364 or 366 of HIV-1 Gag as compared to the sequence of wild type strain NL4-3 or RF.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Bruce Campell/
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